Remarks

After entry of the amendment, claims 1-58 are pending.

The related applications section has been updated.

Claims 1 and 3 have been amended to correct typographical errors in the numbering of the variables.

Claim 3 has been editorially amended to delete the definitions of variables R_7 and R_8 as there is no antecedent basis.

Claim 4 has been amended to clarify that the NSAID compounds of the invention can contain at least one $-NO_2$ group and is supported by the specification at, for example, page 2, lines 17-19 and lines 27-28; page 3, lines 7-8 and lines 26-27; page 4, lines 16-17; page 5, lines 7-8 and lines 17-18; and page 33, lines 3-10.

No issues of new matter should arise and entry of the amendment is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-4 are rejected under 35 USC § 112, first paragraph, as lacking enablement.

Applicants respectfully traverse the rejection and respectfully submit that the claims are fully enabled and one skilled in the art could make and use the presently claimed invention without undue experimentation.

The two aspects of enablement: "making" and "using" the claimed invention are each discussed separately below.

1. Making the Claimed Invention Is Enabled Under 35 USC § 112, First Paragraph.

Contrary to the assertions in the office action, Applicants respectfully submit that the specification has **12** working examples of synthesis for compounds that fall within the scope of the linker X in the compound of Formula I, *see* for example, claim 55. The twelve working examples are:

Examples 17 and 18, at page 79, line 16 to page 81, line 79;

Examples 20-25, at page 82, line 22 to page 89, line 9;

Example 29, at page 92, line 19 to page 94, line 19;

Example 34, at page 98, line 9 to page 99, line 18;

Examples 40 and 41, at page 104, line 15 to page 107, line 14.

Applicants also submit herewith a Declaration under 37 C.F.R. § 1.132 executed by David S. Garvey, Ph.D. (hereafter the "Garvey Declaration"). The Garvey Declaration supports and provides evidence that that one of ordinary skill in this field would be able to make the claimed compounds. In particular, the Garvey Declaration at paragraph 7 states:

> "It is my opinion that one skilled in the art could readily make any and every compound that falls within the scope of the compounds of Formula I in the present application by using readily available materials, such as, for example, the commercially available parent non-steroidal anti-inflammatory compounds, in conventional reactions, in reactions that can be successfully performed by conventional modifications known to one skilled in the art, *e.g.*, by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or by the modification of reactions disclosed in the present application, without undue experimentation."

The Garvey Declaration at paragraph 8 lists numerous issued word-wide patents, patent applications and scientific articles that describe the detailed synthesis of numerous structurally diverse nitrosated nonsteroidal anti-inflammatory compounds

It is Dr. Garvey's opinion that based on the extensive disclosure in the specification and the state of the scientific literature for the synthesis of organic compounds, one skilled in the art would easily be able to prepare any of the compounds disclosed in the present application. *See* Garvey Declaration at paragraph no. 9.

As the Examiner knows, a specification does not have to have any working examples to be enabling. MPEP 2164.02. In any event, Applicants have provided 12 working examples in the specification for making the claimed compounds that are encompassed by the compounds of Formula (I). Additionally Applicants have provided a description with numerous literature references on how one skilled in the art could synthesize the nitrosated compounds of the present invention (see, the specification at, for example, page 41, line 10 to page 42, line 13). Moreover, in the 132 Declaration, Dr. Garvey states that one skilled in the art could make any compound within the scope of the compound of formula I without undue experimentation based on the teachings in the specification.

2. Using the Claimed Invention Is Enabled Under 35 USC § 112, First Paragraph.

Applicants respectfully submit that the use of claimed invention is fully enabled and one skilled in the art could make and use the presently claimed invention without undue experimentation.

The Garvey Declaration at paragraph 10, first sentence, states that "one of skill in the art would readily appreciate that the compounds of Formula (I) are pro-drugs of well known nonsteroidal anti-inflammatory compounds".

In contradistinction to the Examiner's assertion[1], the Garvey Declaration states that "the compounds of Formula (I) would be hydrolyzed under physiological conditions to the parent nonsteroidal anti-inflammatory compound and the linker group of Formula X, substituted with at least one $-NO_2$ group." (*See* the Garvey Declaration at paragraph no. 10, second sentence.) The parent nonsteroidal anti-inflammatory compounds are well known inhibitors of the cyclooxygenase isoenzymes whose biological properties, substrate binding properties, structure activity relationship and methods of use have been extensively studied and described in numerous scientific articles and hence would be easily predictable by one skilled in the art. (*See* Garvey Declaration at paragraph 11.).

The biological properties of the parent nonsteroidal anti-inflammatory compounds have been extensively studied and described in the literature. See for example, Insel, P.A.; Goodman and Gilman, The Pharmacological Basis of Therapeutics, 8th Edition; 638-680 (1990) Pergamon Press, a copy of which is attached hereto. Insel describes the biological properties of numerous nonsteroidal anti-inflammatory compounds, including, but not limited to, their anti-inflammatory, analgesic and antipyretic properties, respiratory properties, cardiovascular effects, gastrointestinal effects, hepatic and renal effects, effects on blood, effects on rheumatic inflammatory and immunological processes, effect on connective tissue, and the like.

As stated in the Garvey Declaration, one skilled in the art will readily appreciate that the linker group of Formula X substituted with at least one $-NO_2$ group, under physiological conditions, would donate, release and/or directly or indirectly transfer nitric monooxide, such

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[1] In the Office Action at page 3, the Examiner asserts that "[t]here is no reasonable basis for the assumption that the myriad of compound embraced by formula (I) will all share the same biological properties."

that the biological activity of the nitrogen monoxide species is expressed at the intended site of action. (*See* Garvey Declaration at paragraph 12.)

Additionally the specification at page 121, line 28 to page 123, line 1, compares the in vivo anti-inflammatory and gastric lesion activity for **29** structurally diverse compounds of the invention. Based on the extensive disclosure in the specification and the fact that the biological properties of the parent nonsteroidal anti-inflammatory compounds have been extensively documented in the literature, one skilled in the art would readily be able to predict the structure-activity relationship of the compounds of the invention.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of lack of enablement, as required in MPEP 2164.04, to maintain the rejection under 35 U.S.C. § 112, first paragraph.

Applicants respectfully submit, in view of the evidence presented in the Garvey Declaration and the comments above, that the claims satisfy the requirements under 35 U. S. C. §112, first paragraph, and respectfully request that the rejections under this provisions be withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph

Claim 4 has been rejected under 35 USC § 112, second paragraph, as being indefinite.

Applicants respectfully submit that the claims satisfy the requirement under 35 U. S. C. § 112, second paragraph.

Claim 4 has been amended to clarify that the nitrosated compounds of the invention are substituted with at least one $-NO_2$ group, i.e. they can contain one or more $-NO_2$ groups.

In view of the above, Applicants respectfully submit that the claims satisfy the requirement under 35 U. S. C. §112, second paragraph, and respectfully request that the rejections under this provision be withdrawn.

Claim Objection

In the office action summary the Examiner has objected to claim 55. However in the detailed action the Examiner has not elaborated on his objection to claim 55. Applicants respectfully request that the Examiner clearly state his objection to claim 55.

Claim 55 lists the names of the compounds from working examples 17, 18, 20-25, 29, 34, 40 and 41 and are all encompassed by the variable X in Formula (I).

Examination of Additional Species

Pursuant to MPEP §803.02, Applicants respectfully request the examination of additional species upon an indication of the allowability of the elected species in claim 1. As stated in the Petition Decision, dated June 15, 2005, on page 3:

> "The examiner must follow MPEP §803.02 and expand the search and examination to additional species until a reasonable number have been considered. Should no prior art be found on any additional species, the entire Group would be considered to avoid the prior art and the claims of the elected Group would be further examined to determine compliance with respect to all other aspects of the statute".

Applicants respectfully request rejoinder of the non-elected species on claim 1, wherein the variable Rn is 1-10, 13-18 and 20-51. As mentioned in the Response and Amendment dated March 30, 2005, the Examiner has already searched other nitrosated non-steroidal anti-inflammatory compounds directed to the non-elected species of the present invention.

Rejoinder of Claims

Applicants respectfully request rejoinder of claims 5-54 and 56-58.

The claims in the pending application are generally directed to nitrosated nonsteroidal anti-inflammatory compounds, and compositions comprising nitrosated nonsteroidal anti-inflammatory compounds, and, optionally, other compounds, kits and the methods of use for the compounds and/or compositions.

If the nitrosated nonsteroidal anti-inflammatory compounds of claims 1-4 are allowable, then all the compositions and kits requiring a nitrosated nonsteroidal anti-inflammatory compounds would also be allowable and all the methods of use for these compositions would also be allowable. In other words every pending claim that requires a **nitrosated nonsteroidal anti-inflammatory compound of claims 1-4** would also be allowable.

Additionally, a search of the prior art for the nitrosated nonsteroidal anti-inflammatory compounds of claims 1-4 would necessarily encompass a search of the prior art for the compositions for the nitrosated nonsteroidal anti-inflammatory compounds, and, optionally, other compounds of claims 29-39, kits of claims 51-54 and their methods of use of claims 5-28 and 40-50. Thus, the prior art for the nitrosated nonsteroidal anti-inflammatory compounds of claims 1-

4, will also be the same prior art for the compositions, kits and methods of use for the nitrosated nonsteroidal anti-inflammatory compounds of claims 1-4.

Applicants respectfully thank the Examiner for his consideration for the rejoinder of claims 5-54 and 56-58.

Conclusion

An early and favorable reconsideration and allowance of the pending claims is respectfully requested. The Examiner is encouraged to contact the undersigned to expedited prosecution of this application.

Respectfully submitted,

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